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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,214	03/19/2004	Arthur M. Brown	T2074-00039	6520

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,214	BROWN ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *10-18 and 21-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,19,20 and 30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-9, 19, 20 and 30-35, without traverse, filed on January 22, 2007, is acknowledged and has been entered. Claims 10-18 and 21-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Accordingly, claims 1-35 are pending. Claims 1-9, 19, 20 and 30-35 are under examination.

Specification

2. In the specification at page 16, last full paragraph, an ampersand appears after "(Aa capture antibody@)" in two occurrences. Please correct or clarify.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-9, 19, 20, and 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step a) is indefinite in reciting, "a first medium" because it appears to denote subsequence of "a second medium". However, there is no recitation of any additional medium in the succeeding method steps or set of claims.

Claim 1, step b) is vague and indefinite in reciting, "effective amount of candidate agent" because the term "effective" is a subjective term that lacks a comparative basis for defining its metes and bounds and there is no statement of what result is to be achieved. Additionally, since claim 1 is drawn to "a method of identifying if an agent alters the level of surface expression of a protein", it is unclear how a [predetermined] effective amount of an unknown candidate agent can be added into the medium containing mammalian cells so as to provide a change in the level of protein expression that can be measured. Please clarify.

Claim 1, step c) is vague and indefinite in reciting, "sufficient amount of time" because the term "sufficient" is a subjective term that lacks a comparative basis for defining its metes and bounds and there is no statement of what result is to be achieved within the time frame.

Claim 1, step d) is vague and indefinite in reciting, "effective amount of fixative" because the term "effective" is a subjective term that lacks a comparative basis for defining its metes and bounds and there is no statement of what result is to be achieved.

Claim 1, step e) lacks clear antecedent basis in reciting, "adding to said first medium" because it is unclear as to whether the recitation intends to refer back to step a) or step b) which recite "first medium", or does it intend to refer back to step d), which

immediately precedes the instant step e), but does not recite "first medium." Please clarify.

Claim 1, step e) is confusing in reciting, "effective amount of at least one antibody" because the term "effective" is a subjective term that lacks a comparative basis for defining its metes and bounds. Additionally, it is unclear how the recitation of "effective amount of at least one" should relatively be interpreted. Please clarify. Same analogous comments and problems apply to the same recitations in claim 2.

Claim 1, step e) is also ambiguous in reciting, "relative to control" because it is unclear as to what elements or reagents are encompassed in the "control." As an example, does the control contain therein a normal level or concentration of the expression protein.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. In this case, it is unclear what elements in claim 1 provides a measure of the level of binding between the antibody and the expression protein in order to allow measurement by fluorescence, luminescence, radioactivity, and absorbance.

Claim 19 is objected to for depending from a non-elected claim.

Claim 19 is ambiguous because it is unclear what role the enzyme plays in relation to the elements and method steps recited in claim 1 from which it depends.

Claim 19 is objected to in lacking antecedent basis in the specification for the recitation of a) "primary and secondary antibody ... coupled to an enzyme" and b)

"primary antibody [or]" ... is coupled to an enzyme". Antecedent basis in the specification only provides that 1) an antibody coupled to an enzyme may be used in direct detection assays whereas 2) a secondary antibody coupled to an enzyme may be used to bind to and provide labeling for a primary antibody that specifically binds antigenic epitope in indirect detection assays.

Claim 20 is objected to for depending from a non-elected claim.

Claim 30 is objected to for depending from non-elected claims.

Claim 31 is objected to for depending from a non-elected claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-9, 19, 20 and 30-35 are rejected on the ground of nonstatutory double patenting over claims 1-9, 19, 20, and 30 of allowed ASN 10/635,010 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: a method of identifying an agent that alters the level of surface expression of integral membrane protein by combining a cell sample with a candidate agent and then contacting the cell mixture with antibody that specifically binds an extracellular epitope of the integral membrane protein. A determination of the difference in level of binding of the extracellular epitope with the antibody between the cell mixture and a normal control provides indication that the candidate agent alters level of surface expression of the protein.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

5. Claims 1-9, 19, 20, and 30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-5 and 7-13 of allowed ASN 10/635,010 in view of Zhang et al. (The Extracellular Domain Suppresses Constitutive Activity of the Transmembrane Domain of the Human TSH

Receptor: Implications for Hormone-Receptor Interaction and Antagonist Design, Endocrinology 141 (9): 3514-3517 (2000)).

Allowed ASN 10/635,010 differs from instant claims 1-9, 19, 20, and 30 in teaching that the mammalian cells express a mutant form of the integral membrane protein.

Zhang et al. provide that TSH receptors (TSHR) are very susceptible to constitutive activation by mutations in various regions of the molecule, including mutations in the extracellular domain (ECD) and extracellular loops of the transmembrane domain. To understand the role of ECD in TSHR, Zhang et al. test several TSHR constructs having major deletions of the ECD.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate application of the method off ASN 10/635,010 with mutant forms of the wild-type extracellular epitope of the integral membrane proteins because Zhang specifically provided that wild-type forms and mutant forms encompass obvious variations of the extracellular epitopes of integral membrane protein that can be differentially studied for ligand-binding activity and constitutive functional activity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-5, 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Woska et al. (US 2002/0068305 A1) in light of Isacke (Integrin α_I, The Adhesion Molecule FactsBook, second edition (2000) 149-151).

Woska et al. provide a method of identifying an agent (chemical compound) that alters (modifies) the level of surface expression of CD11a subunit of LFA-1 protein [0002]. In practice, a medium containing mammalian cells (peripheral blood mononuclear cells) is combined with the agent and then the mixture is incubated for a period of time. Thereafter, the cell mixture is contacted with a labeled antibody that specifically binds the R7.1 (extracellular) epitope of LFA-1 whereupon a fluorescent signal is produced by the binding of the antibody to the R7.1 epitope. In another embodiment, a primary antibody that specifically binds the R7.1 epitope and a secondary labeled antibody the binds the primary antibody may be used whereupon a fluorescent signal is produced by the binding of the antibody to the R7.1 epitope. In either case, the level (increase or decrease) of binding of the R7.1 antibody to the R7.1 epitope of LFA-1 indicates alteration of the surface expression of LFA-1 protein [0011-0014], [0017], [0019], [0021-0023] and [0029]. Woska et al. exemplify treating the cells with a fixative [0639]. Woska et al. disclose application of the method in different assay formats wherein the level of binding is measured by immunofluorescence, radioactivity (radioisotopes), and absorbance [0613], [0616], and [0617]. Enzyme labels that can be used with the method include alkaline phosphatase and horseradish peroxidase [0615]. In as far as the recitation of "at least one extracellular epitope comprises a wild-type epitope" in claim 5, absent any teaching in the Woska reference of the use of cells in

mutant form, it is presumed that the LFA-1 molecules in the cells used by Woska are wild-type.

In as far as the recitation of "the protein is an integral membrane protein", Isacke provides that the CD11a subunit of LFA-1 is an integral, transmembrane cell surface molecule (see page 149). Accordingly, Woska et al. is deemed to anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 6-9 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woska et al. (US 2002/0068305 A1) in light of Isacke (Integrin α_I, The Adhesion

Molecule FactsBook, second edition (2000) 149-151), in view of Zhang et al. (Endocrinology 141 (9): 3514-3517 (2000)).

Woska et al. and Isacke are discussed supra. Woska et al. and Isacke differ from the instant invention in failing to teach that the extracellular epitope contains a tag which replaces at least a portion of an extracellular domain of the protein.

Zhang et al. provide that TSH receptors (TSHR) are very susceptible to constitutive activation by mutations in various regions of the molecule, including mutations in the extracellular domain (ECD) and extracellular loops of the transmembrane domain. To understand the role of ECD in TSHR, Zhang et al. test several TSHR constructs having major deletions (mutations) of the ECD. Specifically, Zhang et al. perform studies on ligand-binding and basal constitutive activation using TSHR tagged at its N-terminus with a hemagglutinin tag, i.e. inserted, recognized by HA-specific monoclonal antibody (see Abstract). The cells are cultured, fixed with paraformaldehyde, and then quantified for expression of HA epitope-tagged TSHR constructs using HA specific monoclonal antibody. Zhang et al. teach using enzyme label (peroxidase) for the method, whereupon enzymatic reaction is measured by Absorbance at 450 nm. (see page 3515, column 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to insert an HA tag recognized by HA specific monoclonal antibody as taught by Zhang into the extracellular domain of the integral membrane protein (LFA-1) taught in the method of Woska because Zhang specifically taught that insertion of HA tag into extracellular domain of the protein provides reliable assessment of ligand-

binding and basal constitutive activities, leading to a better understanding of the role of extracellular domains for integral membrane proteins.

8. Claims 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woska et al. (US 2002/0068305 A1) in light of Isacke (Integrin al, The Adhesion Molecule FactsBook, second edition (2000) 149-151), in view of Owman et al. (US 2002/0150912 A1).

Woska et al. and Isacke are discussed supra. Woska et al. and Isacke differ from the instant invention in failing to teach that the protein contains a fluorescent tag which replaces at least a portion of an intracellular domain of the protein.

Owman et al. provide chimeric reporter constructs, recombinant cells containing the reporter constructs, and assays utilizing the recombinant cells for detection of substances that interact with integral membrane proteins such as G-protein coupled receptors (GPCRs) that act through calcium mobilization and signal through the mitogen-activated protein (MAPK) cascade (see Abstract and [0016] [0018] [0048]. In the high-throughput screening assay, recombinant cells expressing the integral membrane protein are combined with a large number of substances. Interaction with a substance causes the receptor to generate a signal that subsequently activates the reporter gene in the reporter construct, the level of expression of which is monitored using fluorescent or luminescent signal [0072]. The chimeric reporter construct comprises sequences encoding a green fluorescent protein (GFP) inserted at an intracellular domain of the protein [0017] [0056]. According to Owman et al., the

reporter construct and recombinant cells are well-suited for high-throughput screening assays of substances that interact with cell surface receptors. Due to intrinsic fluorescence of GFPs, the need to pre-load substrate molecules in order to detect cells that express the reporter gene is not required; hence, cell handling is simple yet robust for a highly sensitive assay system (see Abstract and [0017].

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the fluorescent tag as taught by Owman into the method of identifying agents that alter cell surface expression of integral membrane protein as taught by Woska because Owman specifically taught that in incorporating use of intrinsic fluorescence of GFPs in cell-based assay systems, the need to pre-load substrate molecules in high-throughput screening assays for substances that interact with cell surface receptors, is not required; hence, cell handling is simple yet robust for a highly sensitive assay system.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gailene R. Gabel
Patent Examiner
Art Unit 1641
March 5, 2007